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Perspective

Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial

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SUMMARY

Objective: The majority of patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have low serum procalcitonin (PCT) values. The aim of this study was to determine whether these patients may benefit from antibiotic treatment.
Methods: A total of 457 patients with AECOPD were screened; 194 patients with AECOPD and PCT <0.1 ng/ml were assigned randomly to an antibiotic group or a control group. In the per-protocol (PP) population, the antibiotic group subjects were required to have used antibiotics for at least 3 days, and the control group subjects were required not to have used antibiotics within the 10 days after admission. The intention-to-treat (ITT) population was defined as the patients who were randomized. The primary outcome was the treatment success rate on day 10 after admission. Secondary outcomes were symptoms assessed on a visual analog scale (VAS), length of hospitalization, mortality, exacerbation rate, and re-hospitalization within 30 days of follow-up (study registered at chictr.org.cn: ChiCTR-TRC-14004726).
Results: 95 patients in the antibiotic group and 96 patients in the control group completed the study. In the ITT population, the overall treatment success rate in the control group (95.8%) was similar to that in the antibiotic group (93.7%), with no significant difference ($p = 0.732$). Five patients in the antibiotic group died, either in hospital or within 30 days of discharge. In the control group, two died within 30 days of discharge. Antibiotic use in the control group was 17.7% (17/96), and age ≥75 years was a predictive risk factor for requiring antibiotic therapy in the control group (odds ratio 4.055, 95% confidence interval 1.297–12.678; $p = 0.012$). According to the PP analysis, the treatment success rate on day 10 after admission was 98.7% (78/79) in the control group and 93.7% (89/95) in the antibiotic group, also with no significant difference ($p = 0.193$). No secondary outcome was significantly different between the two groups.
Conclusion: Antibiotic treatment is no better than placebo in AECOPD with a PCT level <0.1 ng/ml.

1. Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) in China is 8.2% in adults over the age of 40 years.[1] COPD has become an important economic burden for both urban and rural residents all over the world, and the management of acute exacerbations of COPD (AECOPD) increases healthcare costs significantly.[2–4] For patients with AECOPD in the USA and Europe, antibiotic prescription rates of 85%[5] and 86%,[6] respectively, have been reported. Moreover, two retrospective analyses showed that antibiotic treatment benefited patients with AECOPD.[7,8] However, not all patients with AECOPD will benefit from antibiotic therapy,[9,10] and the overuse of antibiotics may increase the risk of microbial resistance.

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In order to reduce antibiotic use in AECOPD patients, a few studies have focused on identifying clinical characteristics and inflammatory biomarkers to guide antibiotic treatment in these patients. Studies have shown that patients with type I Anthonisen exacerbation,[9] purulent sputum,[11,12] and those with very severe lung function impairment requiring invasive or non-invasive mechanical ventilation, are likely to benefit from antibiotic treatment.[13] Procalcitonin (PCT) is a specific biomarker of bacterial infection. It has been studied prospectively as a biomarker to guide antibiotic treatment in patients with AECOPD and lower respiratory tract infections.[14–16] Studies have shown that PCT-guided therapy leads to a reduction in antibiotic use in patients with AECOPD and lower respiratory tract infections.[14–16]

The aim of previous studies on PCT-guided antibiotic therapy in patients with AECOPD and lower respiratory tract infections has been to reduce antibiotic prescription. In these studies, patients with a PCT level of >0.25 ng/ml were considered to have bacterial infections, and antibiotic treatment was encouraged. A level of 0.1 to 0.25 ng/ml was considered to indicate a possible bacterial infection, and antibiotics were discouraged or encouraged according to the stability of the patient's clinical condition. A PCT level of 0.1 ng/ml or less was considered to indicate the absence of bacterial infection, and the use of antibiotics was discouraged.[14–16] However, a subgroup analysis showed that patients with AECOPD and a PCT level of <0.1 ng/ml benefited from treatment with doxycycline.[17] Therefore, the value of antibiotic treatment for hospitalized AECOPD patients with low serum PCT values is controversial.

It was hypothesized that antibiotic treatment would benefit AECOPD patients with a PCT level of <0.1 ng/ml. In order to confirm this hypothesis, a single-center, prospective randomized controlled trial was conducted. The study was registered at chictr.org.cn (ChiCTR-TRC-14004726).

2. Materials and methods

2.1. Study design and objectives

From June 10, 2014 to September 5, 2015, all patients with AECOPD admitted to the Department of Respiratory and Critical Care Medicine of Beijing Luhe Hospital were screened. A diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 criteria was required. AECOPD was defined as an acute change in symptoms that were beyond normal day-to-day variation and that required a change in daily therapeutic drug regimen.[2] All patients included in this study were classified into Anthonisen type I to type III.[9] Patients with AECOPD who were ≥40 years of age, had sound understanding and language abilities, and who had a PCT level <0.1 ng/ml were included. Exclusion criteria were fever (≥38.0 °C), tracheal intubation within 24 h after hospital admission, a PCT level of ≥0.1 ng/ml on admission, pneumonia, chronic renal failure, history of malignant disease, immunosuppressive therapy, and refusal to participate. The study protocol was approved by the Ethics Committee of Luhe Hospital (Institutional Review Board approval number 2014-01), and all patients provided written informed consent.

A computer digital table method was used to generate randomization numbers. Researchers in this study had 24-h access to randomization numbers, allowing immediate and concealed allocation to the trial. Each patient was allocated a unique trial number. Persons responsible for allocation concealment were not allowed to be involved in the measurement of results. Eligible patients were assigned randomly to either the control group or the antibiotic group.

Antibiotics were withheld from patients in the control group. However, antibiotics could be administered later for patients whose clinical condition was unstable[16] or who had a worsening of symptoms and signs, and for those with positive evidence of bacteria as assessed by the attending physicians. In the antibiotic group, antibiotics were administered routinely. In order to cover the most common pathogenic bacteria, piperacillin–sulbactam (CR Double-Crane Pharmaceuticals Co., Ltd) was selected as the first choice of antibiotic; ceftazidime (Hainan Haiyao Pharmaceuticals Co., Ltd) or levofloxacin (CR Double-Crane Pharmaceuticals Co., Ltd) was substituted in the case of a penicillin allergy. Antibiotic agents could be adjusted according to microbial culture results and depending on the recommendations of the attending physicians. The duration of antibiotic treatment was also determined by the attending physicians. Other treatment methods in the two groups were instituted by the attending physicians in accordance with the GOLD guidelines.

2.2. Measurement

The baseline characteristics of the patients with AECOPD were collected on the day of hospital admission. PCT was measured using an immunoluminescence assay (VIDAS BRAHMS PCT) within 2 h after hospitalization. C-reactive protein (CRP) was measured by the immune turbidity method. Blood was collected for routine laboratory examinations, and chest computed tomography (CT) was performed within 48 h of hospitalization. Lung function tests were performed by trained technicians upon hospital admission and on the day of hospital discharge according to the guidelines of the American Thoracic Society.[18]

Symptoms were assessed by the patients themselves on a visual analog scale (VAS); the symptoms assessed included dyspnea, cough, fatigue, and sputum purulence.[19] The symptom VAS score was obtained upon hospital admission, at 3 days after hospitalization, and on the day of discharge. The assessment scale ranged from 0 (feeling completely healthy) to 10 (feeling extremely sick).

Treatment efficacy was evaluated by per-protocol (PP) and intention-to-treat (ITT) analysis on day 10 after hospitalization. In the PP population, the antibiotic group subjects were required to have used antibiotics for at least 3 days, and the control group subjects were required not to have used antibiotics within the 10 days after admission. The ITT population was defined as all patients who were randomized.

Treatment success was defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs associated with the exacerbation, without new symptoms or signs). Treatment failure was defined as a worsening of symptoms and signs or death.[20] Telephone follow-up was performed on day 30 after hospital discharge. Follow-up assessments included exacerbations, re-admission, antibiotic use, and death.

The primary outcome was the treatment success rate on day 10 after admission. The secondary outcomes included symptoms assessed by VAS (at hospital admission, 3 days after hospitalization, and on the day of hospital discharge), the length of hospital stay, intubation rate, mortality during hospitalization and in the 30-day follow-up period, the rate of antibiotic use, and re-admission due to AECOPD within the 30-day follow-up period.

2.3. Statistical analysis

SPSS version 17.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for data management and the statistical analysis. Measurement data were expressed as the mean ± standard deviation, while categorical data were presented as a number or percentage. An independent samples *t*-test was applied to compare the difference in measurement data between groups; for comparisons of enumeration data, the Pearson Chi-square test or continuous correction Chi-square test was used. Binary logistic regression

analysis was used to assess the following risk factors for patients in the control group who needed antibiotic therapy: sex, smoking status, frequent hospitalization in the previous year (≥2 times), age ≥75 years, bronchiectasis, coronary heart disease, hypertension, diabetes, chronic congestive heart failure, history of cerebral infarction, oxygen therapy, home non-invasive mechanical ventilation treatment, antibiotic use within 3 months prior to hospitalization, sputum purulence, Anthonisen type, respiratory failure, non-invasive ventilation during hospitalization, respiratory intensive care unit admission, tracheal intubation, serum CRP values >40 mg/l,[21] elevated plasma fibrinogen, positive bacterial culture of sputum or endotracheal aspirate, and systemic corticosteroid treatment. The odds ratio (OR) and 95% confidence interval (CI) were calculated for risk factors. All tests were two tailed; a *p*-value of <0.05 was considered significant.

A study found that the efficacy of moxifloxacin treatment for patients with chronic bronchitis and AECOPD was 95%.[22] A subgroup analysis in another study showed that the clinical success rate in the antibiotic group was 18% higher than that in the placebo group for AECOPD with a PCT level <0.1 ng/ml,[17] and another study found that the success rate in the antibiotic group was 14% higher than that in the placebo group.[21] Based on these studies, it was estimated that the clinical success rate at 10 days after hospital admission would be 95% in the antibiotic group and 80% in the control group. With an α error of 0.05 and a power of 0.80, and using MedCalc 15.0 statistical software to calculate the sample size, it was determined that 88 cases would be needed in each arm. Considering a 10% dropout rate, the ideal sample size was calculated to be 194 patients in total. Thus, 194 patients with AECOPD were assigned randomly to, and evenly split between, the antibiotic and control groups according to the computer digital table method.

3. Results

3.1. Subjects

A total 457 patients with AECOPD were screened at the time of hospital admission. Of these, 97 had a PCT level ≥0.1 ng/ml: 42 had a PCT level of 0.1–0.25 ng/ml and 55 had a PCT level >0.25 ng/ml. These patients were excluded, along with a further 166 patients for other reasons (Figure 1).

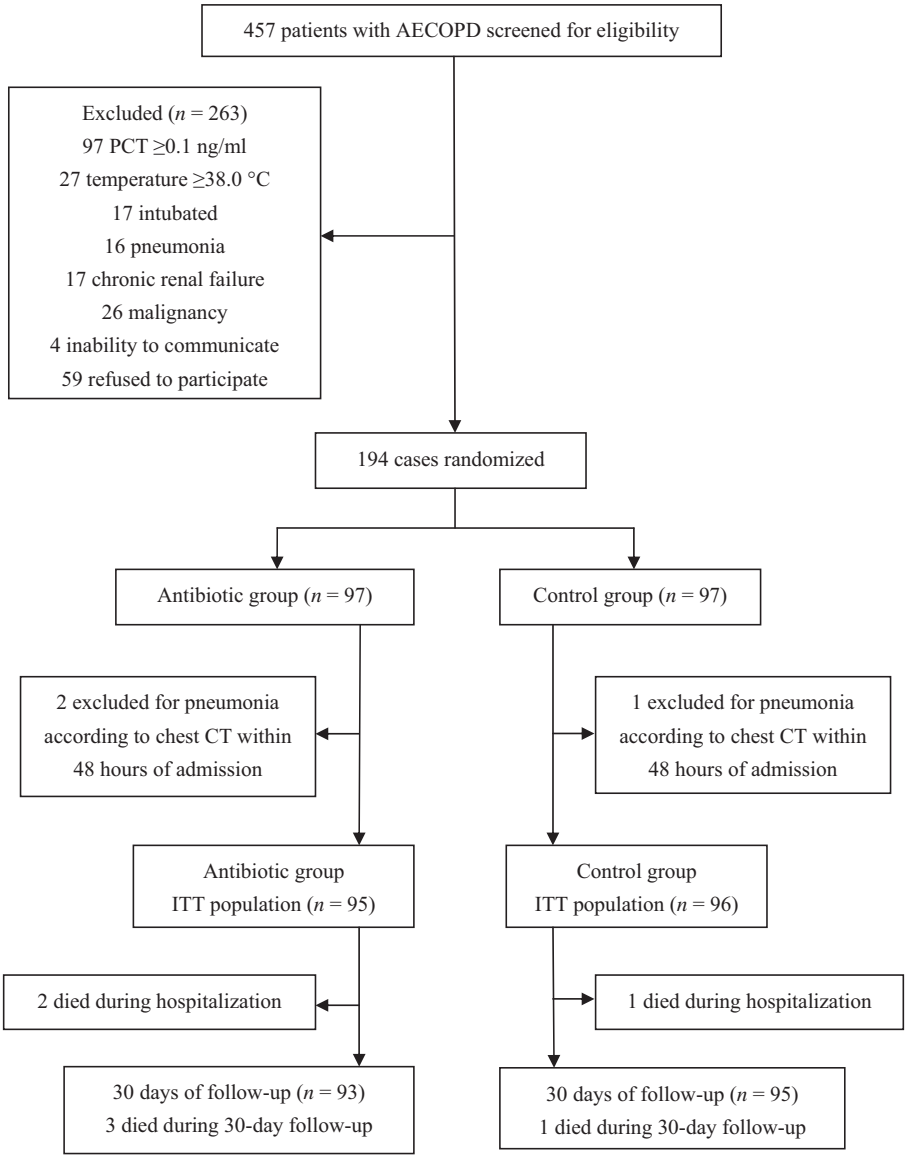

Figure 1. Study flow diagram (AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PCT, procalcitonin; ITT, intention-to-treat).

During the study period, 194 patients met the inclusion criteria and were assigned randomly, with even distribution, to the antibiotic group and control group. Two patients in the antibiotic group and one patient in the control group were confirmed to have pneumonia by chest CT within 48 h after hospital admission and dropped out. The remaining 95 cases in the antibiotic group and 96 cases in the control group completed the study; no patient was lost during the 30-day follow-up period.

3.2. Demographic characteristics

The baseline characteristics of randomized patients are shown in Table 1. There was no significant difference between the two groups with regard to age, sex, smoking status, frequent hospitalizations due to AECOPD in the previous year (≥2 times), Anthonisen type, sputum purulence, antibiotic use within 3 months prior to admission, bronchiectasis, coronary heart disease, hypertension, diabetes, history of cerebral infarction, chronic congestive heart failure, respiratory failure, respiratory intensive care unit admission, or systemic corticosteroid use.

Lung function parameters of forced expiratory volume in one second, forced vital capacity, and the ratio of forced expiratory volume in one second to forced vital capacity, and arterial blood gas analysis values of pH, PaO_2, and $PaCO_2$, were taken on hospital admission and the day of hospital discharge. There was no significant difference in these values between the antibiotic group and control group (Tables 2 and 3).

3.3. Clinical efficacy analysis

In the antibiotic group, 76 cases received piperacillin–sulbactam treatment, 18 cases received ceftazidime treatment, and one patient received levofloxacin treatment. Seventeen patients in the control group were prescribed antibiotics after 3 days by the attending physicians due to their clinical condition; piperacillin–sulbactam was given to 13 patients and ceftazidime to four.

Table 1
Baseline characteristics of 191 patients randomized to the antibiotic and control groups[a]

Characteristics	Antibiotic group ($n=95$)	Control group ($n=96$)	p-Value
Age, years	73.4 ± 10.1	72.5 ± 9.2	0.482
Age ≥75 years	51 (53.7)	46 (47.9)	0.425
Male	67 (70.5)	70 (72.9)	0.714
Smoking			
Former	79 (83.2)	82 (85.4)	0.668
Current	18 (18.9)	28 (29.2)	0.099
Frequent admissions in the previous year (≥2)	22 (23.2)	20 (20.8)	0.698
Anthonisen type[b]			
Type I	25 (26.3)	22 (22.9)	0.586
Type II	56 (58.9)	56 (58.3)	0.931
Type III	14 (14.7)	18 (18.8)	0.458
Type I and type II with sputum purulence	25 (26.3)	23 (24.0)	0.707
Sputum purulence	25 (26.3)	23 (24.0)	0.707
Domiciliary oxygen therapy	22 (23.2)	20 (20.8)	0.698
Home mechanical ventilation	6 (6.3)	8 (8.3)	0.593
Antibiotic use prior to admission within 3 months	49 (51.6)	42 (43.9)	0.279
Comorbidities			
Bronchiectasis	22 (23.2)	20 (20.8)	0.698
Coronary heart disease	31 (32.9)	33 (34.4)	0.799
Hypertension	46 (43.8)	46 (47.9)	0.559
Diabetes	15 (15.8)	13 (13.5)	0.661
Chronic congestive heart failure	28 (29.5)	22 (22.9)	0.303
History of cerebral infarction	6 (6.3)	12 (12.5)	0.144
Respiratory failure	37 (38.9)	37 (38.5)	0.954
Mechanical ventilation	23 (24.2)	22 (22.9)	0.833
Mechanical ventilation without purulent sputum	16 (16.8)	17 (17.7)	0.874
Respiratory intensive care unit admission	21 (22.1)	17 (17.7)	0.447
Systemic corticosteroid use	39 (45.9)	49 (51.0)	0.488
Respiratory rate, beats/min	21.6 ± 2.7	21.2 ± 3.0	0.322
Heart rate, beats/min	89.7 ± 18.5	88.7 ± 18.0	0.730
Systolic blood pressure, mmHg	136.2 ± 18.2	135.7 ± 15.7	0.827
Diastolic blood pressure, mmHg	79.4 ± 12.1	79.5 ± 10.4	0.943

[a] Data are presented as the mean ± standard deviation, or number (%).
[b] Type I: all of the Anthonisen criteria are present (increased dyspnea, increased sputum volume, and purulent sputum); type II: only two criteria present; type III: only one criterion present.

Table 2
Comparison of lung function between the groups in the intention-to-treat population[a]

	Day of admission		p-Value	Day of discharge		p-Value
	Antibiotic ($n=95$)	Control ($n=96$)		Antibiotic ($n=59$)	Control ($n=69$)	
FEV_1 (% pre)	36.7 ± 15.8	38.4 ± 16.5	0.494	44.9 ± 20.8	46.6 ± 19.0	0.627
FVC (% pre)	48.7 ± 19.5	45.5 ± 17.5	0.284	54.3 ± 20.5	56.8 ± 20.3	0.493
FEV_1/FVC	57.9 ± 14.4	60.3 ± 14.9	0.277	59.0 ± 14.1	59.9 ± 12.7	0.703

FEV_1 (% pre), forced expiratory volume in one second (percentage of predicted); FVC (% pre), forced vital capacity (percentage of predicted); FEV_1/FVC, ratio of forced expiratory volume in one second to forced vital capacity.
[a] Data are presented as the mean ± standard deviation.

Table 3
Comparison of arterial blood gas analysis values between the groups in the intention-to-treat population[a]

	Day of admission		*p*-Value	Day of discharge		*p*-Value
	Antibiotic ($n=95$)	Control ($n=96$)		Antibiotic ($n=78$)	Control ($n=64$)	
pH value	7.43 ± 0.06	7.42 ± 0.07	0.187	7.45 ± 0.05	7.45 ± 0.05	0.940
$PaCO_2$, mmHg	46.6 ± 13.5	49.3 ± 17.3	0.240	44.5 ± 10.9	44.4 ± 11.9	0.946
PaO_2, mmHg	89.3 ± 30.7	83.9 ± 19.9	0.162	84.6 ± 18.6	86.4 ± 22.7	0.613
Oxygenation index	332 ± 97	321 ± 87	0.417	338 ± 89	344 ± 86	0.382

[a] Data are presented as the mean ± standard deviation.

When applying the ITT analysis, the overall treatment success rate in the control group (92/96, 95.8%) was similar to that in the antibiotic group (89/95, 93.7%), with no significant difference between the two groups (Table 4) ($p = 0.732$). Six patients in the antibiotic group were considered treatment failures on day 10 after admission. Furthermore, five of them died either in hospital or within 30 days of discharge. In the control group, four did not reach treatment success on day 10 after admission and two died within 30 days of discharge.

According to the PP analysis, all 95 patients in the antibiotic group completed at least 3 days of antibiotics and 79 patients in the control group did not receive antibiotics within 10 days after admission. The treatment success rate on day 10 after admission was 98.7% (78/79) in the control group and 93.7% (89/95) in the antibiotic group, with no significant difference ($p = 0.193$).

The other 17 patients in the control group were given antibiotics by the attending physicians (antibiotic use 17.7%) for reasons including worsening of symptoms or signs (six cases) and no improvement in symptoms or signs (11 cases). For these 17 patients, the average time from admission to receiving antibiotics was 4.6 ± 1.8 days. Three of these 17 cases did not reach treatment success on day 10 after admission and one of them died. Binary logistic regression analysis showed that age ≥75 years was a risk factor associated with requiring antibiotic treatment in the control group (OR 4.055, 95% CI 1.297–12.678; $p = 0.012$).

There was no significant difference between the antibiotic group and control group with regard to symptoms assessed by VAS, the length of hospital stay, intubation rate, mortality during hospitalization and during the 30 days of follow-up, re-hospitalization due to AECOPD, and antibiotic use in the 30 days after hospital discharge (ITT analysis, Table 4).

4. Discussion

Bacterial and viral infections are important factors in AECOPD. Studies on the effect of antibiotics in patients with AECOPD have been inconsistent. Patients admitted to intensive care units with severe AECOPD are expected to benefit from antibiotic treatment; however, this remains to be determined for patients with less severe AECOPD admitted to general wards.[10] The GOLD guidelines suggest that antibiotics should be given to patients with AECOPD who fall into three categories: (1) those who have the three cardinal symptoms of an increase in dyspnea, sputum volume, and sputum purulence; (2) those who have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; and (3) those who require invasive or non-invasive mechanical ventilation.[2]

Currently, most patients admitted to a hospital with AECOPD receive antibiotic therapy.[5,6] In order to reduce the use of antibiotics in this population, PCT has been employed as a specific marker of bacterial infection to guide antibiotic treatment. There have been only a few studies on PCT-guided antibiotic treatment for patients with AECOPD. One study showed that PCT-guided antibiotic treatment reduced antibiotic prescriptions from 72% to 40%.[15] Moreover, lung function at 2 weeks and at 6 months, the rate of re-hospitalization due to AECOPD, and the number of days between AECOPD episodes were similar in the two groups.[15] Two other studies of PCT-guided antibiotic treatment for lower respiratory tract infections also found that PCT-guided antibiotic treatment decreased antibiotic exposure and that clinical outcomes did not differ between the PCT-guided group and the standard group.[14,16] Previous studies on PCT-guided antibiotic treatment for patients with AECOPD have used a PCT level of >0.25 ng/ml to indicate the need for antibiotic therapy; in these studies, the aim was to reduce antibiotic exposure.[10,15] In reality, PCT values are usually low in most patients with AECOPD; about 51–75% of patients have a PCT <0.1 ng/ml,[15,17] and only 7–20% of patients have a PCT level of >0.25 ng/ml.[15,17,23] So far, there have been no reports on whether antibiotic treatment is of benefit to AECOPD patients with low PCT levels.

In this study, the percentage of patients with a PCT of <0.1 ng/ml was 78.8% (360/457). It was hypothesized that patients with AECOPD and a PCT of <0.1 ng/ml may benefit from antibiotic therapy. Moreover, in order to guarantee the authenticity of this study, broad-spectrum antibiotics that cover common pathogens

Table 4
Clinical outcomes in the intention-to-treat population[a]

Outcomes	Antibiotic ($n=95$)	Control ($n=96$)	*p*-Value
VAS			
Day of hospital admission	19.5 ± 8.3	18.8 ± 7.7	0.562
3 days after admission	13.4 ± 7.2	12.6 ± 4.9	0.415
Day of hospital discharge	6.1 ± 4.9	5.5 ± 3.8	0.405
Success rate at day 10	89 (93.7)	92 (95.8)	0.732
Length of hospital stay, days	10.9 ± 8.1	9.9 ± 5.1	0.310
Intubation	1 (1.1)	2 (2.1)	1.000
AECOPD in the 30 days after hospital discharge	17 (17.9)	11 (11.5)	0.209
Re-admission within 30 days of hospital discharge	13 (13.7)	8 (8.3)	0.237
Antibiotic use within 30 days of hospital discharge	17 (17.9)	12 (12.5)	0.299
Death during hospitalization or within 30 days of follow-up	5 (5.63)	2 (2.1)	0.242

VAS, visual analog scale; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.
[a] Data are presented as the mean ± standard deviation, or number (%).

including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were selected for treatment. To determine if antibiotic treatment is beneficial in terms of a more rapid improvement in symptoms, patients were taught to conduct a self-rating VAS for four main symptoms: dyspnea, fatigue, cough, and sputum purulence.

However, it was found that patients in the control group achieved a similar treatment success rate with less antibiotic use compared with the patients in the antibiotic group. What is more, five patients in the antibiotic group died as compared to two patients in the control group, although the difference was not significant. Based on these results, it is suggested that antibiotics be withheld initially from patients with AECOPD and a PCT level of <0.1ng/ml; whether and when antibiotics should be added to the patient's treatment protocol should be guided by the patient's clinical condition and determined by the attending physician. This strategy will provide an ideal treatment success rate without any short-term adverse clinical outcomes.

Studies have shown that sputum purulence and CRP ≥40 mg/dl are predictive risk factors for treatment failure in patients with AECOPD,[23] and sputum purulence-guided antibiotic therapy can be used in patients with AECOPD.[11,12] In the present study, using binary logistic regression analysis, it was found that only age ≥75 years was a predictive risk factor for requiring antibiotic treatment in the control group (OR 4.055, 95% CI 1.297–12.678; $p = 0.012$); sputum purulence and CRP ≥40 mg/dl may not be the indications for antibiotic use in patients with AECOPD and PCT values <0.1 ng/ml.

This study had several limitations. First, antibiotic use 3 months prior to admission in patients was high. The reason for this is that many patients with AECOPD in China often choose to take antibiotics at home. Second, the follow-up assessment was only conducted over 30 days. Long-term outcome evaluations are needed. Third, although piperacillin–sulbactam, ceftazidime, and levofloxacin are broad-spectrum antibiotics, none of them covers all pathogens. For instance, they do not cover methicillin-resistant *Staphylococcus aureus* or multidrug-resistant *Acinetobacter baumannii*. Piperacillin–sulbactam and ceftazidime are ineffective against atypical pathogens such as *Mycoplasma pneumoniae*, and ceftazidime and levofloxacin are ineffective against multidrug-resistant *P. aeruginosa*. Finally, this study did not involve patients with PCT in the range of 0.1–0.25 ng/ml; whether these patients could benefit from antibiotic treatment also needs to be studied further.

In conclusion, in this randomized clinical trial it was found that antibiotic treatment was no better than placebo in AECOPD patients with a PCT level <0.1 ng/ml.

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Ethical approval: The study protocol was approved by the Ethics Committee of Luhe Hospital.

Conflict of interest: We declare that no conflicts of interest exist.

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